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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Michael L Goldman
Nixon Peabody LLP
Clinton Square
PO Box 31051
Rochester, NY 14603

EXAMINER
HORLICK, KENNETH R

ART UNIT	PAPER NUMBER
1637	10

DATE MAILED: 09/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/640,882	Applicant(s) HALL, BARRY G.	
	Examiner KENNETH HORLICK	Art Unit 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *Amendment A 6/24/02* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-63* is/are pending in the application.

4a) Of the above claim(s) *44-63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10, 12, 13, 15-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. Applicant's election with traverse of Group I in Paper No. 9 is acknowledged. The traversal is on the ground(s) that the recited Groups are related and would require common areas of search, and thus that no serious burden exists. This is not found persuasive because the different classifications of the groups, and the specific reasons that the subject matter of the different groups are distinct (as detailed in the Restriction Requirement), do in fact support a conclusion of undue search burden.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 44-63 are still withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

3. **NEW GROUND OF REJECTION NECESSITATED BY THE AMENDMENT**

Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim is confusing because it depends from cancelled claim 14.

MAINTAINED REJECTIONS AND REPLY TO ARGUMENTS

4. Claims 1-3 and 16-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims are confusing because it cannot be determined what actions are required in claim 1 in "determining whether the mutant resistance gene is likely to evolve through two or more independent mutation events". It is submitted that the further limitation recited in claim 4, which clarifies said "determining", is required in order for one of ordinary skill in the art to understand what is being claimed.

5. With respect to the above rejection, the arguments of the response filed 06/19/02 have been fully considered, but are not found persuasive. It is stated in the response that claim 1 has been clarified such that it is not indefinite; the Office does not agree. Specifically, it cannot be determined what active steps other than those set forth in dependent claim 4 are encompassed by the "determining" language of claim 1.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-10, 12, 13, and 15-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Melnick et al. (any one of US 6,063,562, US 5,766,842, or WO 96/08580).

Claims 1-10, 12, 13, and 15-23 are drawn to methods comprising providing a host cell comprising a mutant resistance gene and determining whether the mutant resistance gene is likely to evolve through two or more independent mutation events. Claims 24-34 are drawn to screening methods comprising providing a host cell comprising a mutant anti-pathogenic resistance gene, growing the host cell on a selection media containing a candidate drug, and determining growth of the host cell on the selection media. Claims 35-43 are drawn to methods comprising providing a resistance gene ineffective against a candidate drug, introducing multiple mutations into said gene, and determining the minimum number of mutations required to overcome the activity of the drug.

The '562 patent discloses methods which "may be used, for example, to identify, prior to clinical use, resistant biologically-active mutant forms of a protein which may emerge in response to the clinical use of a particular antimicrobial agent. In particular, the present method may be use to predict, prior to clinical use, all possible first-generation biologically-active resistant mutants which may emerge in response to the

clinical use of a particular antimicrobial agent." Further, said methods "may also be used, for example, to evaluate, prior to clinical use, the ultimate efficacy of an inhibitor contemplated for use against the protein." Bacteria and viruses are specifically mentioned as pathogenic organisms for which drug resistance was a well-known problem. Cell culture selection is taught as a means known in the art for evaluating potential antimicrobial agents. Melnick et al. note that their invention "is premised on the discovery that, in many instances, there are only a very small number of distinct initial evolutionary pathways that a protein can take in order to escape sensitivity to an effective inhibitory drug targeted thereagainst". The methods of '562 involve creating a comprehensive library of mutations in a resistance gene, wherein the mutant genes encode a protein which differs from the original protein "by at least one, and preferably no more than three, amino acid substitutions", and isolating and characterizing mutants which provide for resistance. The methods are applicable "in the screening of prospective drugs". The '562 patent further discloses that single mutations may lead to enhanced resistance, and that two or more mutations may independently provide such resistance, and further that two or more mutations may act in concert to produce such resistance. To characterize mutant genes with two or more mutations, the '562 patent discloses creating new sets of appropriate single or multiple mutants which will allow determination of exactly which mutation(s) are involved in resistance. See entire '562 patent, especially abstract, columns 1-4, columns 8-11, and columns 13-19. Corresponding teaching are present in the '842 patent and WO document.

While Melnick et al. disclose all of the above, they do not appear to teach them all within a single embodiment (hence this rejection under 35 USC 103 and not under 35 USC 102).

One of ordinary skill in the art would have been motivated to characterize mutations in microbial resistance genes which might evolve in response to drugs by: introducing mutations into a resistance gene, and screening for resistant mutants in a host cell system, because this was clearly suggested by the combined teachings of Melnick et al. Applications of this system in drug screening and in determining drug efficacy (i.e., longevity) are directly suggested by them as well. While a preferred embodiment of Melnick et al. involves HIV protease and a non-host cell screening system, the broader teachings as noted above in combination with the key concept of creating mutant libraries and systematically identifying new resistance mutations would have led the skilled artisan to what is being claimed. It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods.

7. With respect to the above rejection, the arguments of the response filed 06/19/02 have been fully considered, but are not found persuasive. The response argues that the Melnick et al. references describe performing a single round of mutagenesis and then identifying those mutants that exhibit resistance, and that these references do not teach or suggest methods comprising successive rounds of mutagenesis and selection until no further enhancement of the resistance phenotype is perceived.

The Office does not agree for the following reasons. In columns 18-19 of the '562 patent, for example, Melnick et al. disclose carrying out first-generation mutagenesis, and then based upon the analysis of these mutants, creating a new first and/or second set of mutants. The "determining" steps of instant claim 4 are taught in column 18, lines 20-39. Melnick et al. also teach the detection of "combination" resistance-conferring mutations involving two or more amino acid substitutions, and repetitive screening procedures to test all possible combinations of substitutions for resistance-conferring properties. It is submitted that these teachings of Melnick et al. cannot be distinguished from the "successive rounds of mutagenesis" step(s) in the instant claims.

8. No claims are free of the prior art.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kenneth R Horlick whose telephone number is 703-308-3905. The examiner can normally be reached on Monday-Thursday 6:30AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Kenneth R. Horlick, Ph.D.
Kenneth R Horlick
Primary Examiner
Art Unit 1637

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September 11, 2002